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59. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;

comprising the steps of:

- A
- (a) identifying an atom of the interface region, comprising the steps of:
    - (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
    - (2) irradiating a nucleus of an atom of the CL;
    - (3) identifying in a multidimensional NMR experiment an NMR cross-peak between said CL and said SL, thereby identifying a CL reactive region immediately adjacent to the SL;
    - (4) irradiating a nucleus of an atom of the CL reactive region identified in step (3); and

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- (5) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of said enzyme that is perturbed by the irradiation of the nucleus of the CL reactive region, thereby identifying an atom of the interface region; then
- (b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:
- (1) binding a CL mimic to the CL site of said enzyme;
  - (2) irradiating the nucleus of the interface atom identified in step (a); and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

60. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as atoms of an SL, if bound to the enzyme;

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wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;

comprising the steps of:

(a) identifying an atom of the interface region, comprising the steps of:

- (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
- (2) irradiating a nucleus of an atom of the CL; and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak between said CL and said SL, thereby identifying a CL reactive region immediately adjacent to the SL and an interface region of said SL; then

(b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

- (1) binding a CL mimic to the CL site of said enzyme and said SL to the SL site of said enzyme;
- (2) irradiating the nucleus of the interface atom identified in step (a); and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation

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of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

61. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;

comprising the steps of:


- (a) identifying an atom of the interface region, comprising the steps of:
- (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
  - (2) irradiating a nucleus of an atom of the SL;
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak between said CL and said SL,

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thereby identifying an SL reactive region immediately adjacent to the CL;

- (4) irradiating a nucleus of an atom of the SL reactive region identified in step (3); and
- (5) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of said enzyme that is perturbed by the irradiation of the nucleus of the SL reactive region, thereby identifying an atom of the interface region; then

(b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

- 
- (1) binding a CL mimic to the CL site of said enzyme;
  - (2) irradiating the nucleus of the interface atom identified in step (a); and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

62. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme; wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

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wherein an interface region is defined as atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;

comprising the steps of:

- A
- (a) identifying an atom of the interface region, comprising the steps of:
    - (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
    - (2) irradiating a nucleus of an atom of the SL; and
    - (3) identifying in a multidimensional NMR experiment an NMR cross-peak between said CL and said SL, thereby identifying an SL reactive region immediately adjacent to the CL and an interface region of said SL; then
  - (b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:
    - (1) binding a CL mimic to the CL site of said enzyme and said SL to the SL site of said enzyme;
    - (2) irradiating the nucleus of the interface atom identified in step (a); and

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- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

63. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;


comprising the steps of:

- (a) identifying an atom of the interface region, comprising the steps of:
- (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;

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- (2) irradiating a nucleus of an atom of the CL;
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak between an atom of said CL and an atom of said SL; and an NMR cross-peak between said atom of said CL, or an atom proximal to said CL atom, and an atom of said enzyme, thereby identifying a CL reactive region immediately adjacent to the SL and an atom of the interface region; then

- (b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

- 
- (1) binding a CL mimic to the CL site of said enzyme;
  - (2) irradiating the nucleus of the interface atom identified in step (a); and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

64. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site



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(CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);


wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;

comprising the steps of:

(a) identifying an atom of the interface region, comprising the steps of:

- 
- (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
  - (2) irradiating a nucleus of an atom of the SL; and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak between an atom of said CL and an atom of said SL; and an NMR cross-peak between said atom of said SL, or an atom proximal to said SL atom, and an atom of said enzyme, thereby identifying an SL reactive region immediately adjacent to the CL and an atom of the interface region; then

(b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

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- (1) binding a CL mimic to the CL site of said enzyme;
- (2) irradiating the nucleus of the interface atom identified in step (a); and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

65. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as CL atoms immediately adjacent to the SL;


comprising the steps of:

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(a) identifying an atom of the interface region, comprising the steps of:

- (1) binding an SL to the SL site of said enzyme;
- (2) irradiating a nucleus of an atom of the SL reactive region; and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of said enzyme that is perturbed by the irradiation of the nucleus of the SL reactive region, thereby identifying an atom of the interface region; then

(b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

- 
- (1) binding a CL mimic to the CL site of said enzyme;
  - (2) irradiating the nucleus of the interface atom identified in step (a); and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

66. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

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wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as the reactive atom of the CL and CL atoms immediately adjacent to the SL;

comprising the steps of:

- A (
- (a) identifying an atom of the interface region, comprising the steps of:
    - (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme, thereby forming an enzyme-CL-SL complex;
    - (2) irradiating one or more nuclei of atoms of said enzyme-CL-SL complex and obtaining an NMR spectrum;
    - (3) binding a chemically modified CL to the CL site of the enzyme and said SL to the SL site of said enzyme, wherein the modification is to an atom of the CL reactive region, and then repeating the same NMR experiment; and

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- (4) comparing the spectra from steps (a)(2) and (a)(3) to identify an NMR cross-peak corresponding to a nucleus that is affected by the chemical modification, thereby identifying an atom of the interface region; then
- (b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:
- (1) binding a CL mimic to the CL site of said enzyme;
- (2) irradiating the nucleus of the interface atom identified in step (a); and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.
- A (

67. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

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wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and

wherein a CL reactive region is defined as the reactive atom of the CL and CL atoms immediately adjacent to the SL;

comprising the steps of:

- (a) identifying an atom of the interface region, comprising the steps of:
- (1) binding a CL to the CL site of said enzyme and an SL to the SL site of said enzyme;
  - (2) irradiating a nucleus of an atom of the SL;
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak between an atom of said CL and an atom of said SL; and an NMR cross-peak between said atom of said SL, or an atom proximal to said SL atom, and an atom of said enzyme, thereby identifying an SL reactive region immediately adjacent to the CL and an atom of the interface region;
  - (4) binding a chemically modified CL to the CL site of the enzyme, wherein the modification is to an atom of the CL reactive region, and then repeating the same NMR experiment; and
  - (5) comparing the spectra from steps (a) (3) and (a) (4) to identify an NMR cross-peak corresponding to a nucleus that is affected by the chemical

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modification, thereby identifying an SL reactive region immediately adjacent to the CL and an atom of the interface region; then

(b) identifying an atom in a CL mimic that is proximal to the interface region, comprising the steps of:

- (1) binding a CL mimic to the CL site of said enzyme;
- (2) irradiating the nucleus of the interface atom identified in step (a); and
- (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

68. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme binds a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and binds a specificity ligand (SL) at an adjacent specificity ligand site (SL site);


wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL if bound to the enzyme;

wherein the enzyme catalyzes a reaction involving the SL and a reactive atom of the CL;

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wherein a CL reactive region immediately adjacent to the SL has been identified and wherein an atom of the interface region has been identified;

comprising the steps of:

- 
- (1) binding a CL mimic to the CL site of said enzyme;
  - (2) irradiating the nucleus of the identified atom of the interface region; and
  - (3) identifying in a multidimensional NMR experiment an NMR cross-peak corresponding to a nucleus of the CL mimic that is perturbed by the irradiation of the interface nucleus, thereby identifying an atom of the CL mimic that is proximal to the interface region.

69. (New) A method for identifying an atom of a common ligand mimic that is proximal to an interface region of an enzyme;

wherein the enzyme can bind a common ligand (CL) or a common ligand mimic (CL mimic) at a common ligand site (CL site) and can bind a specificity ligand (SL) at an adjacent specificity ligand site (SL site);

wherein an interface region is defined as the atoms of the enzyme between the CL site and SL site, and atoms of an SL, if bound to the enzyme;

wherein the enzyme can catalyze a reaction involving the SL and a reactive atom of the CL; and



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wherein a CL reactive region immediately adjacent to the SL has been identified and wherein an atom of the interface region has been identified;

comprising the steps of:

- A
- (1) binding a CL mimic to the CL site of said enzyme, and then performing a multidimensional NMR experiment;
  - (2) binding a CL mimic to the CL site of a chemically modified enzyme, wherein the modification is isotopic labeling at the atom of the interface region that has been identified, and then repeating the same NMR experiment;
  - (3) comparing the spectra from steps (1) and (2) to identify an NMR cross-peak corresponding to a nucleus that is affected by the chemical modification, thereby identifying an atom of the CL mimic that is proximal to the interface region.

70. (New) The method of claim 59, wherein the enzyme has a monomer molecular weight greater than 20 kD.

71. (New) The method of claim 70, wherein the enzyme has a monomer molecular weight greater than 35 kD.

72. (New) The method of claim 59, wherein the enzyme has a complete molecular weight greater than 50 kD.

73. (New) The method of claim 72, wherein the enzyme has a complete molecular weight greater than 100 kD.

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74. (New) The method of claim 59, wherein the enzyme is from a human pathogen.

75. (New) The method of claim 59, wherein the enzyme is from bacteria.

76. (New) The method of claim 59, wherein the enzyme is a dehydrogenase.

77. (New) The method of claim 59, wherein the enzyme is a kinase.

78. (New) The method of claim 59, wherein the CL is a cofactor.

79. (New) The method of claim 78, wherein the CL is ubiquitin.

80. (New) The method of claim 78, wherein the CL is SAM (S-adenosyl methionine).

81. (New) The method of claim 78, wherein the cofactor contains a nucleotide.

82. (New) The method of claim 81, wherein the CL is NAD+.

83. (New) The method of claim 81, wherein the CL is NADH.

84. (New) The method of claim 81, wherein the CL is NADP+.

85. (New) The method of claim 81, wherein the CL is NADPH.

86. (New) The method of claim 81, wherein the CL is ATP.

87. (New) The method of claim 81, wherein the CL is ADP.

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88. (New) The method of claim 59, wherein the CL is farnesyl-pyrophosphate.

89. (New) The method of claim 59, wherein the CL is geranyl-pyrophosphate.

90. (New) The method of claim 59, wherein the CL is geranyl-geranyl-pyrophosphate.

91. (New) The method of claim 59, wherein the NMR cross-peak is identified by the cross-peak undergoing an intensity or shape change.

A ( 92. (New) The method of claim 59, wherein the NMR cross-peak is identified by a relaxation effect.

93. (New) The method of claim 59, wherein the NMR cross-peak is identified by the cross-peak undergoing a chemical shift change.

94. (New) The method of claim 59, wherein an NMR cross-peak is identified using a multidimensional multinuclear method, wherein the transfer of magnetization to protons is only to or from amide protons.

95. (New) The method of claim 59, wherein an NMR cross-peak is identified using a multidimensional multinuclear method, wherein the detectable atoms are the NH protons of protein at an amino acid selected from the group consisting of Asn, Gln, Arg and His.

96. (New) The method of claim 59, wherein an NMR cross-peak is identified using a multidimensional multinuclear method, wherein the detectable atoms are the methyl protons of protein specifically  $^{13}\text{C}$ - $^1\text{H}$ , labeled at an amino acid selected from the group consisting of Leu, Thr, Ile, Val, Ala and Met.

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97. (New) The method of claim 59, wherein an NMR cross-peak is identified using a multidimensional multinuclear NMR method that includes a  $^1\text{H}$ - $^{15}\text{N}$  correlation.

98. (New) The method of claim 97, wherein the NMR method is a  $^1\text{H}$ - $^{15}\text{N}$  correlation and nuclear Overhauser enhancement spectroscopy experiment.

99. (New) The method of claim 59, wherein an NMR cross-peak is identified using a multidimensional multinuclear NMR method that includes a  $^1\text{H}$ - $^{13}\text{C}$  correlation.

100. (New) The method of claim 99, wherein the NMR method is an HNCA experiment.

101. (New) The method of claim 59, wherein an NMR cross-peak is identified using an NMR method that includes a  $\{^1\text{H}, ^1\text{H}\}$  NOESY step.

102. (New) The method of claim 101, further comprising the step of introducing a third dimension for  $^{15}\text{N}$  or  $^{13}\text{C}$  chemical shift.

103. (New) The method of claim 101, wherein a diagnostic  $^1\text{H}$ - $^{13}\text{C}$  or  $^1\text{H}$ - $^{15}\text{N}$  one bond coupling constant is obtained without decoupling to a heteroatom in one of the two dimensions.

104. (New) The method of claim 101, further comprising the step of using 2D  $^{13}\text{C}$ - $^1\text{H}$  or  $^{15}\text{N}$ - $^1\text{H}$  HMQC or HSQC- $\{^1\text{H}, ^1\text{H}\}$  NOESY.

105. (New) The method of claim 59, wherein an NMR cross-peak is identified using an NMR experiment that uses transverse relaxation-optimized spectroscopy (TROSY), whereby narrow line widths are achieved.

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106. (New) The method of claim 59, wherein an NMR cross-peak is identified using an NMR experiment that uses deuterium labeling, whereby narrow line widths are achieved.

107. (New) The method of claim 59, wherein immediately adjacent is within 5 Ångströms.

A (108. (New) The method of claim 59, wherein immediately adjacent is within 4 Ångströms.

109. (New) The method of claim 63, wherein the atom of the interface region identified in step (a) is an atom of the enzyme.

110. (New) The method of claim 63, wherein the atom of the interface region identified in step (a) is an atom of an SL bound to the enzyme.

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REMARKS

Claims 1-58 have been canceled. New claims 59-110 have been added. Support for the new claims can be found throughout the specification and the claims as filed. In particular, support for the new claims can be found, for example, in original claims 1-46 and on page 13, lines 1-23; page 18, lines 19-34; page 19, lines 9-28; page 22, lines 8-24; and page 27, line 29, to page 28, line 7. Accordingly, these new claims do not raise an issue of new matter and entry thereof is respectfully requested.